Clinical trial results:
A Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare the Pharmacokinetics, Efficacy and Safety between CT-P10, Rituxan and MabThera in Patients with Rheumatoid Arthritis

Summary

EudraCT number	2013-004555-21
Trial protocol	AT LV PT DE SK HU GR
Global end of trial date	25 January 2017

Results information

Result version number	v1 (current)
This version publication date	04 January 2018
First version publication date	04 January 2018

Trial information

Trial identification

Sponsor protocol code	CT-P10 3.2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02149121
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celltrion, Inc.
Sponsor organisation address	23 Academy-ro (13-6, Songdo-dong), Yeonsu-gu, Incheon, Korea, Republic of, 22014
Public contact	Clinical Operations Management Department, CELLTRION, Inc., +82 32 850 6724, SuEun.Song@celltrion.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Part 1 of the study is:
• To evaluate and compare pharmacokinetics in terms of area under the serum concentration-time curve from zero to time of last quantifiable concentration (AUC0-last), AUC from zero to infinity (AUC0-∞) and maximum serum concentration (Cmax) (after the second infusion) of CT-P10 to Rituxan, CT-P10 to MabThera and Rituxan to MabThera during the first course of treatment (over the first 24 weeks).

The primary objective of Part 2 of the study is:

• To demonstrate that CT-P10 is similar to Rituxan and MabThera in terms of efficacy as determined by clinical response according to change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (C-reactive protein [CRP]) at Week 24.

Protection of trial subjects:

Hypersensitivity had been assessed by vital sign monitoring on each dosing day and recorded on each dosing day at the following time points:

• Before administration (within 15 minutes prior to the beginning of the study drug infusion)
• Within 15 minutes after the end of the study drug infusion
• 1 hour (±15 minutes) after the end of the study drug infusion

In addition, hypersensitivity should be monitored by routine continuous clinical monitoring including 12-lead ECG monitoring 1 hour (±15 minutes) after the end of the study drug infusion.
Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator must be available.
For patients who experience or develop life threatening infusion related anaphylactic reactions, study treatment must be stopped immediately and the patient withdrawn from the study.

Background therapy:

Methotrexate will be administered at a dosage of between 7.5 and 25 mg orally or parenterally every week (dose and route must be maintained from beginning to study end). Folic acid will be administered at a dosage of at least 5 mg/week for as long as MTX treatment is continued.

Evidence for comparator:

CT P10 is being developed as a biosimilar candidate of Rituxan and MabThera, a compound with established efficacy in its registered indications and CT-P10 is intended to offer a more affordable treatment than Rituxan and MabThera, if similar efficacy and safety can be demonstrated during the conduct of these key clinical studies.

Actual start date of recruitment	06 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Bosnia and Herzegovina: 34
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Ukraine: 38
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	Colombia: 18
Country: Number of subjects enrolled	Mexico: 41
Country: Number of subjects enrolled	Peru: 63
Country: Number of subjects enrolled	Korea, Republic of: 24
Worldwide total number of subjects	372
EEA total number of subjects	103

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	326
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient randomly assigned to treatment: 06 August 2014
A toal of 98 study centers were initiated in Europe, Asia Pacific, and Latin America.

Pre-assignment

Screening details:

Key Inclusion Criteria
1.Patient is male or female between 18 and 75 years old, inclusive
2.Patient has a diagnosis of RA according to the revised 1987 ACR classification criteria for at least 6 months prior to randomization
3.Patient has experienced an inadequate or intolerance response to previous treatment with the antitumor necrosis factor

Pre-assignment period milestones

Number of subjects started	495[1]
Intermediate milestone: Number of subjects	Subject screened: 495
Intermediate milestone: Number of subjects	Enrolled: 372
Number of subjects completed	372

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening Failure: 111
Reason: Number of subjects	GCP non-compliant site: 12

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The 'Number of subjects reported to have started the pre-assignment period' means subjects who consented to participate in this trial through the Screening procedure. If these subjects meet Inclusion and Exclusion criteria defined by the protocol, they can be randomized which will have study drug administration. Subject who received at least 1 dose of study drug (CT-P10, Rituxan or MabThera) is considered as 'Enrolled' in the trial.

Period 1

Period 1 title	Main Study Period-1st treatment course
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P10

Arm description:

CT-P10 (1000mg) coadministered with MTX between 7.5 and 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)

Arm type	Experimental
Investigational medicinal product name	CT-P10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

CT-P10 (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Arm title	Rituxan

Arm description:

US-licensed reference product. Rituxan (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)

Arm type	Active comparator
Investigational medicinal product name	Rituxan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rituxan (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Arm title	MabThera

Arm description:

EU-approved reference product. MabThera (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)

Arm type	Active comparator
Investigational medicinal product name	MabThera
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MabThera (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Number of subjects in period 1	CT-P10	Rituxan	MabThera
Started	161	151	60
Completed	145	142	58
Not completed	16	9	2
Consent withdrawn by subject	7	4	1
Physician decision	1	-	-
Adverse event, non-fatal	2	4	1
Patient died	1	-	-
Lost to follow-up	1	-	-
Lack of efficacy	2	1	-
Protocol deviation	2	-	-

Period 2

Period 2 title	Main Study Period-2nd treatment course
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P10

Arm description:

CT-P10 (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)

Arm type	Experimental
Investigational medicinal product name	CT-P10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

CT-P10 (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Arm title	Rituxan

Arm description:

US-licensed reference product. Rituxan (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)

Arm type	Active comparator
Investigational medicinal product name	Rituxan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rituxan (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Arm title	MabThera

Arm description:

EU-approved reference product. MabThera (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)

Arm type	Active comparator
Investigational medicinal product name	MabThera
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MabThera (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Number of subjects in period 2[2]	CT-P10	Rituxan	MabThera
Started	142	138	58
Completed	140	134	56
Not completed	2	4	2
Consent withdrawn by subject	1	1	-
Developed any malignancy	-	1	1
Adverse event, non-fatal	-	1	-
Lost to follow-up	1	1	-
Lack of efficacy	-	-	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Seven subjects did not initiated the 2nd course after completion of the 1st course. Among them, 4 subjects did not meet safety criteria for the 2nd course initiation (each 2 subjects from the CT-P10 and Rituxan groups), and were monitored up to Week 48. The other 3 subjects were discontinued after Week 24 and entered as "discontinued after course 2, not treated" in Period 2 Section (1 subject in CT-P10: withdrew consent; 2 subjects in Rituxan: 1 lack of efficacy and 1 disease progression).

Period 3

Period 3 title	Extension Study Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P10 maintenance

Arm description:

Patients who were assigned to receive CT-P10 for their first infusion in the study were considered to be CT-P10 maintenance and continued to receive CT-P10 for the treatment course in the Extension Study Period. CT-P10 (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week)

Arm type	Experimental
Investigational medicinal product name	CT-P10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

CT-P10 (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Arm title	Rituxan maintenance

Arm description:

Patients who were assigned to receive Rituxan for their first infusion in the study were assigned again at Extension Week 0 to Rituxan maintenance group, who continued to receive Rituxan for the treatment course of the Extension Study PEriod. Rituxan (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week)

Arm type	Active comparator

Investigational medicinal product name	Rituxan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rituxan (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Arm title	Switched from Rituxan

Arm description:

Patients who were assigned to receive Rituxan for their first infusion in the study were assigned again to Switched from Rituxan group and received CT-P10 for the treatment course of the Extension study period. CT-P10 (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week).

Arm type	Active comparator
Investigational medicinal product name	CT-P10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

CT-P10 (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Arm title	Switched from MabThera

Arm description:

Patients who were assigned to receive MabThera for their first infusion in the study were considered to be Switched from MabThera group and received CT-P10 for the treatment course of the Extension study period. CT-P10 (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week)

Arm type	Active comparator
Investigational medicinal product name	CT-P10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

CT-P10 (1000mg), MTX (between 7.5 to 25 mg/week, oral or parenteral dose), folic acid (≥ 5mg/week)

Number of subjects in period 3[3]	CT-P10 maintenance	Rituxan maintenance	Switched from Rituxan
Started	122	64	62
Completed	121	64	60
Not completed	1	0	2
Consent withdrawn by subject	1	-	2

Number of subjects in period 3[3]	Switched from MabThera
Started	47
Completed	47
Not completed	0
Consent withdrawn by subject	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: According to the protocol, only the eligible subjects can be participated in the Extension Study Period. When the subjects had completed the Main Study Period, and met the predefined safety criteria based on the results assess within 8 weeks from Week 0 of the Extension Study period, subjects could continue on to the Extension Study Period with an additional treatment course. Due to the ineligibility of evaluation result, some of subjects were not enrolled in the Extension study period.

Baseline characteristics

Reporting groups	
Reporting group title	CT-P10
Reporting group description:	
CT-P10 (1000mg) coadministered with MTX between 7.5 and 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	Rituxan
Reporting group description:	
US-licensed reference product. Rituxan (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	MabThera
Reporting group description:	
EU-approved reference product. MabThera (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	

Reporting group values	CT-P10	Rituxan	MabThera
Number of subjects	161	151	60
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	143	127	56
From 65-84 years	18	24	4
85 years and over	0	0	0
Age continuous Units: years			
median	53.0	53.0	51.5
full range (min-max)	18 to 74	21 to 74	20 to 74
Gender categorical Units: Subjects			
Female	138	130	50
Male	23	21	10

Reporting group values	Total		
Number of subjects	372		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		

Adolescents (12-17 years)	0		
Adults (18-64 years)	326		
From 65-84 years	46		
85 years and over	0		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	318		
Male	54		

End points

End points reporting groups

Reporting group title	CT-P10
Reporting group description:	
CT-P10 (1000mg) coadministered with MTX between 7.5 and 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	Rituxan
Reporting group description:	
US-licensed reference product. Rituxan (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	MabThera
Reporting group description:	
EU-approved reference product. MabThera (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	CT-P10
Reporting group description:	
CT-P10 (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	Rituxan
Reporting group description:	
US-licensed reference product. Rituxan (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	MabThera
Reporting group description:	
EU-approved reference product. MabThera (1000mg) coadministered with MTX between 7.5 to 25 mg/week (oral or parenteral dose) and folic acid (≥ 5mg/week)	
Reporting group title	CT-P10 maintenance
Reporting group description:	
Patients who were assigned to receive CT-P10 for their first infusion in the study were considered to be CT-P10 maintenance and continued to receive CT-P10 for the treatment course in the Extension Study Period. CT-P10 (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week)	
Reporting group title	Rituxan maintenance
Reporting group description:	
Patients who were assigned to receive Rituxan for their first infusion in the study were assigned again at Extension Week 0 to Rituxan maintenance group, who continued to receive Rituxan for the treatment course of the Extension Study PEriod. Rituxan (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week)	
Reporting group title	Switched from Rituxan
Reporting group description:	
Patients who were assigned to receive Rituxan for their first infusion in the study were assigned again to Switched from Rituxan group and received CT-P10 for the treatment course of the Extension study period. CT-P10 (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week).	
Reporting group title	Switched from MabThera
Reporting group description:	
Patients who were assigned to receive MabThera for their first infusion in the study were considered to be Switched from MabThera group and received CT-P10 for the treatment course of the Extension study period. CT-P10 (1000mg) coadministered with MTX between 7.5 to 25mg/week (oral or parenteral dose) and folic acid (≥ 5mg.week)	
Subject analysis set title	All-randomized population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The all-randomized population consisted of all patients enrolled and randomly assigned to receive a dose of study drug, regardless of whether or not any study drug dosing was completed.	

Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population of the Main Study Period consisted of all patients who received 2 full doses (Week 0 and Week 2) of the study drug and provided at least 1 post-treatment PK concentration result during the first course of treatment in the Main Study Period.
Note. The PK population was the primary population for the summary of PK data.

Subject analysis set title	Efficacy Population
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy population for the Main Study Period consisted of all patients who received at least 1 full dose (1000 mg) of study drug and provided at least 1 post-treatment efficacy result during the first course of treatment in the Main Study Period

Subject analysis set title	Pharmacodynamic Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD population for the Main Study Period consisted of all patients who received at least 1 full dose (1000 mg) of study drug and provided at least 1 post-treatment PD result during the first course of treatment in the Main Study Period.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all patients who received at least 1 (full or partial) dose of study drug during any dosing period.

Subject analysis set title	All-randomized - Extension Study Period subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The “all-randomized population – Extension Study Period subset” consisted of all patients in the all-randomized population who received at least 1 (full or partial) dose of study drug in the Extension Study Period.

Subject analysis set title	Efficacy - Extension Study Period subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The “efficacy – Extension Study Period subset” consisted of all patients in the efficacy population who received at least 1 full dose (1000 mg) of study drug and provided at least 1 post-treatment efficacy result during the Extension Study Period.

Subject analysis set title	Pharmacodynamic - Extension Study Period subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The “pharmacodynamic – Extension Study Period subset” consisted of all patients in the PD population who received at least 1 full dose (1000 mg) of study drug and provided at least 1 post-treatment PD result during the Extension Study Period.

Subject analysis set title	Safety - Extension Study Period subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The “safety – Extension Study Period subset” consisted of all patients in the safety population who received at least 1 (full or partial) dose of study drug during the Extension Study Period.

Subject analysis set title	CT-P10: 1st treatment course in the Main Study Period
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set received an infusion of study drug (CT-P10) at Week 0 and Week 2 of the 1st treatment course in the Main Study Period.

Subject analysis set title	Reference products: 1st treatment course in Main Study Period
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set received an infusion of reference products (Rituxan and MabThera) at Week 0 and Week 2 of the 1st treatment course in the Main Study Period.

Subject analysis set title	Rituxan: 1st treatment course in Main Study Period
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set received an infusion of reference product (Rituxan) at Week 0 and Week 2 of the 1st treatment course in the Main Study Period.

Subject analysis set title	MabThera: 1st treatment course in Main Study Period
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set received an infusion of reference product (MabThera) at Week 0 and Week 2 of the 1st treatment course in the Main Study Period.

Primary: AUC0-last

End point title	AUC0-last

End point description:

AUC0-last: Area under the concentration-time curve from time 0 to the last measurable concentration.
Note: Measure Type is geometric least squares mean.

End point type	Primary

End point timeframe:

over the first 24 weeks

End point values	CT-P10: 1st treatment course in the Main Study Period	Rituxan: 1st treatment course in Main Study Period	MabThera: 1st treatment course in Main Study Period	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62[1]	60[2]	59[3]	
Units: h*µg/mL				
geometric mean (standard error)	162414.81 (± 1.073)	167309.07 (± 1.073)	172450.97 (± 1.075)	

Notes:

[1] - Pharmacokinetics population

[2] - Pharmacokinetics population

[3] - Pharmacokinetics population

Statistical analyses

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - AUC0-last

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of AUC0-last, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v Rituxan: 1st treatment course in Main Study Period

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Parameter estimate	Ratio of geometric least square means
Point estimate	97.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.08
upper limit	106.99

Notes:

[4] - Equivalence margin: 80%-125%

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - AUC0-last

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of AUC0-last, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v MabThera: 1st treatment course in Main Study Period
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	equivalence[5]
Parameter estimate	Ratio of geometric least square means
Point estimate	94.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	85.4
upper limit	103.86

Notes:

[5] - Equivalence margin: 80%-125%

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - AUC0-last

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of AUC0-last, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	Rituxan: 1st treatment course in Main Study Period v MabThera: 1st treatment course in Main Study Period
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Parameter estimate	Ratio of geometric least square means
Point estimate	103.07

Confidence interval	
level	90 %
sides	2-sided
lower limit	93.32
upper limit	113.85

Notes:

[6] - Equivalence margin: 80%-125%

Primary: AUC0-inf

End point title	AUC0-inf

End point description:

AUC0-inf: Area under the concentration-time curve from time 0 extrapolated to infinity
Note: Measure Type is geometric least squares mean.

End point type	Primary

End point timeframe:

over the first 24 weeks

End point values	CT-P10: 1st treatment course in the Main Study Period	Rituxan: 1st treatment course in Main Study Period	MabThera: 1st treatment course in Main Study Period	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	59[7]	60[8]	56[9]	
Units: h*ug/mL				
geometric mean (standard error)	162377.28 (± 1.068)	169480.80 (± 1.069)	180637.81 (± 1.072)	

Notes:

[7] - Pharmacokinetics population

[8] - Pharmacokinetics population

[9] - Pharmacokinetics population

Statistical analyses

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - AUC0-inf

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of AUC0-inf, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v Rituxan: 1st treatment course in Main Study Period
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	equivalence[10]
Parameter estimate	Ratio of geometric least square means
Point estimate	95.81

Confidence interval	
level	90 %
sides	2-sided
lower limit	87.39
upper limit	105.04

Notes:

[10] - Equivalence margin: 80%-125%

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - AUC0-inf

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of AUC0-inf, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v MabThera: 1st treatment course in Main Study Period
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	equivalence[11]
Parameter estimate	Ratio of geometric least square means
Point estimate	89.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	81.85
upper limit	98.72

Notes:

[11] - Equivalence margin: 80%-125%

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - AUC0-inf

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of AUC0-inf, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	Rituxan: 1st treatment course in Main Study Period v MabThera: 1st treatment course in Main Study Period
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence[12]
Parameter estimate	Ratio of geometric least square means
Point estimate	106.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.03
upper limit	117.08

Notes:

[12] - Equivalence margin: 80%-125%

Primary: Cmax

End point title	Cmax

End point description:

Cmax: Observed maximum concentration after the second infusion
Note: Measure Type is geometric least squares mean.

End point type	Primary

End point timeframe:

over the first 24 weeks

End point values	CT-P10: 1st treatment course in the Main Study Period	Rituxan: 1st treatment course in Main Study Period	MabThera: 1st treatment course in Main Study Period	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62[13]	59[14]	59[15]	
Units: ug/mL				
geometric mean (standard error)	367.03 (± 1.042)	386.65 (± 1.042)	412.40 (± 1.043)	

Notes:

[13] - Pharmacokinetics population

[14] - Pharmacokinetics population

[15] - Pharmacokinetics population

Statistical analyses

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - Cmax

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of Cmax, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v Rituxan: 1st treatment course in Main Study Period
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	equivalence[16]
Parameter estimate	Ratio of geometric least square means
Point estimate	94.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.61
upper limit	100.55

Notes:

[16] - Equivalence margin: 80%-125%

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - Cmax

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of Cmax, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v MabThera: 1st treatment course in Main Study Period
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	equivalence[17]
Parameter estimate	Ratio of geometric least square means
Point estimate	89
Confidence interval	
level	90 %
sides	2-sided
lower limit	84.01
upper limit	94.28

Notes:

[17] - Equivalence margin: 80%-125%

Statistical analysis title	Co-primary Pharmacokinetics Endpoints - Cmax

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of Cmax, Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Point estimates (geometric means and ratio of geometric means) and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

Comparison groups	Rituxan: 1st treatment course in Main Study Period v MabThera: 1st treatment course in Main Study Period
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	equivalence[18]
Parameter estimate	Ratio of geometric least square means
Point estimate	106.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	100.56
upper limit	113.13

Notes:

[18] - Equivalence margin: 80%-125%

Primary: Change from baseline of DAS28 (CRP)

End point title	Change from baseline of DAS28 (CRP)

End point description:

Note: Measure Type is adjusted least squares mean.

End point type	Primary

End point timeframe:

Week 24

End point values	CT-P10: 1st treatment course in the Main Study Period	Reference products: 1st treatment course in Main Study Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	138[19]	196[20]		
Units: Score				
least squares mean (standard error)	-2.13 (± 0.175)	-2.09 (± 0.176)		

Notes:

[19] - Efficacy population

[20] - The combined Rituxan and MabThera treatment groups. Efficacy population

Statistical analyses

Statistical analysis title	Co-primary Efficacy Endpoint - CFB of DAS28 (CRP)

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value: change from baseline of DAS28 (CRP), Fixed effect: treatment group, Covariates: gender, region, race, prior anti-TNF-α blocker status, and RF or anti-CCP status.
Adjusted least squares means and standard error, estimate of treatment difference [CT-P10 - (Reference products)] and 2-sided 95% confidence interval calculated from the ANCOVA model.

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v Reference products: 1st treatment course in Main Study Period
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	equivalence[21]
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.21

Notes:

[21] - Equivalence margin: +/- 0.60

Secondary: B-cell counts

End point title	B-cell counts

End point description:

Note: Measure Type is geometric least squares mean.

End point type	Secondary

End point timeframe:

up to 24 weeks

End point values	CT-P10: 1st treatment course in the Main Study Period	Reference products: 1st treatment course in Main Study Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123[22]	173[23]		
Units: cells/mcL				
geometric mean (standard error)	25.30 (± 1.073)	24.66 (± 1.072)		

Notes:

[22] - Pharmacodynamic population

[23] - The combined Rituxan and MabThera treatment groups. Pharmacodynamic Population

Statistical analyses

Statistical analysis title	Secondary Pharmacodynamics endpoint-B-cell kinetic

Statistical analysis description:

Analysis Method: Analysis of covariance (ANCOVA).
Response value:log transformed values of B-cell kinetics, Fixed effect: treatment group, Covariates:baseline result, gender, region, race, prior anti-TNF-α blocker status and RF or anti-CCP status.
Estimate of Geometric Least Square Mean and ratio of Geometric Least Square Means (CT-P10 / reference products) were obtained from back transforming the least square means from the ANCOVA

Comparison groups	CT-P10: 1st treatment course in the Main Study Period v Reference products: 1st treatment course in Main Study Period
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric least square means
Point estimate	102.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	92.86
upper limit	113.39

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 48 weeks (Main Study Period)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	CT-P10

Reporting group description:

The safety population consisted of all patients who received at least 1 (full or partial) dose of study drug during any dosing period.

Reporting group title	Rituxan

Reporting group description: -

Reporting group title	MabThera

Reporting group description: -

Serious adverse events	CT-P10	Rituxan	MabThera
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 161 (8.07%)	14 / 151 (9.27%)	4 / 60 (6.67%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangioma			
subjects affected / exposed	0 / 161 (0.00%)	0 / 151 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			

subjects affected / exposed	0 / 161 (0.00%)	0 / 151 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	4 / 161 (2.48%)	2 / 151 (1.32%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 161 (0.00%)	2 / 151 (1.32%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 161 (0.62%)	0 / 151 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 161 (0.62%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 161 (0.00%)	0 / 151 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 161 (0.62%)	0 / 151 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 151 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 151 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 161 (0.62%)	0 / 151 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 161 (0.62%)	0 / 151 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand deformity			
subjects affected / exposed	1 / 161 (0.62%)	0 / 151 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 161 (0.62%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 161 (0.00%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 161 (0.62%)	1 / 151 (0.66%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	CT-P10	Rituxan	MabThera
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 161 (69.57%)	83 / 151 (54.97%)	35 / 60 (58.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 161 (3.11%)	7 / 151 (4.64%)	0 / 60 (0.00%)
occurrences (all)	5	10	0

Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	33 / 161 (20.50%)	12 / 151 (7.95%)	13 / 60 (21.67%)
occurrences (all)	39	15	15
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 161 (3.73%)	4 / 151 (2.65%)	0 / 60 (0.00%)
occurrences (all)	6	5	0
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 161 (4.97%)	8 / 151 (5.30%)	2 / 60 (3.33%)
occurrences (all)	9	9	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 161 (3.73%)	5 / 151 (3.31%)	2 / 60 (3.33%)
occurrences (all)	7	5	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 161 (2.48%)	5 / 151 (3.31%)	1 / 60 (1.67%)
occurrences (all)	4	6	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 161 (1.86%)	1 / 151 (0.66%)	3 / 60 (5.00%)
occurrences (all)	3	1	3
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 161 (0.62%)	1 / 151 (0.66%)	2 / 60 (3.33%)
occurrences (all)	1	1	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 161 (3.11%)	4 / 151 (2.65%)	1 / 60 (1.67%)
occurrences (all)	5	5	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	24 / 161 (14.91%)	30 / 151 (19.87%)	9 / 60 (15.00%)
occurrences (all)	32	31	12
Urinary tract infection			

subjects affected / exposed	15 / 161 (9.32%)	8 / 151 (5.30%)	2 / 60 (3.33%)
occurrences (all)	23	14	2
Lower respiratory tract infection			
subjects affected / exposed	10 / 161 (6.21%)	7 / 151 (4.64%)	3 / 60 (5.00%)
occurrences (all)	11	9	3
Rhinitis			
subjects affected / exposed	3 / 161 (1.86%)	6 / 151 (3.97%)	1 / 60 (1.67%)
occurrences (all)	4	6	1
Influenza			
subjects affected / exposed	2 / 161 (1.24%)	0 / 151 (0.00%)	2 / 60 (3.33%)
occurrences (all)	2	0	2
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	7 / 161 (4.35%)	4 / 151 (2.65%)	1 / 60 (1.67%)
occurrences (all)	7	5	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2013	Summary of significant changes included the following: • Downgraded ACR20 as a secondary endpoint. • Clarified follow-up of B-cell, IgM and IgG monitoring. • Clarified the schedule of infusions in the second treatment course. • Other administrative changes.
02 June 2014	Summary of significant change included the following: • Changed equivalence margin of DAS28 from 0.75 to 0.6 to reflect recommendation from the Committee for Medicinal Products for Human Use and other regulatory agencies. • Updated sections regarding statistical analysis according to the update of DAS28 margin. • Added AUC0-day14 as one of secondary PK endpoints to reflect recommendation from the Food and Drug Administration. • Added mean change in DAS28 at Week 12 as one of secondary efficacy endpoints to reflect recommendation from the European Medicines Agency. • Combined Rituxan and MabThera groups for the Part 2 analyses. • Added a section for diagnosis of anaphylactic reactions based on the Sampson criteria (Sampson et al., 2006). • Clarified EOS visit. • Other administrative changes.
05 August 2015	Summary of significant changes included the following: • Revised to have additional course of treatment with single transition to evaluate additional safety and efficacy. • Other administrative changes.
11 March 2016	Summary of significant changes includes the followings: • Updated covariates of ANCOVA for PK and efficacy primary endpoints and the comparison of the concentration of B-cell counts to include clinically relevant variables at baseline. • Updated Section to prepare additional clinical study report(s) by regulatory or academic purpose and to remove a report to be developed for data from each patient up to Week 48. • Other administrative changes.
29 March 2016	Summary of significant changes included the following: • Updated covariates of ANCOVA for PK and efficacy primary endpoints and the comparison of the concentration of B-cell counts to include clinically relevant variables at baseline. • Updated Section to prepare additional clinical study report(s) by regulatory or academic purpose and to remove a report to be developed for data from each patient up to Week 48. • Added immunogenicity sampling time points at Extension Weeks 8 and 16 for further evaluation of immunogenicity in the Extension Study Period. • Other administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: